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Clustering of Metabolic Syndrome Traits Is Associated With Maladaptive Carotid Remodeling and Stiffening

A 6-Year Longitudinal Study

Isabel Ferreira, Hanneke J. Beijers, Fleur Schouten, Yvo M. Smulders, Jos W. Twisk, Coen D. Stehouwer

Abstract—Maladaptive arterial remodeling may constitute a mechanism underlying the risk of stroke in individuals with the metabolic syndrome (MetS), but evidence supporting this contention derives from cross-sectional studies only. We, therefore, investigated, in apparently healthy adults, whether changes in MetS status between the ages of 36 and 42 years (never [n=207, reference group], incident [n=31], recovery [n=23], and persistent [n=32]) were associated with changes in carotid interadventitial diameter, lumen diameter, intima-media thickness, circumferential wall tension and stress, and Young's elastic modulus. All data analyses were adjusted for sex, height, and (changes in) age, lifestyle variables, low-density lipoprotein cholesterol, and use of antihypertensive medication. At baseline and as compared with the reference group, individuals with persistent MetS had significantly higher interadventitial diameter, circumferential wall tension, circumferential wall stress, and Young's elastic modulus but not intima-media thickness. In the course of follow-up, these individuals (versus reference group) displayed significantly steeper increases in intima-media thickness (0.011 versus 0.005 mm/y), which were accompanied by significantly steeper increases in interadventitial diameter (0.077 versus 0.032 mm/y) and lumen diameter (0.055 versus 0.023 mm/y) but not circumferential wall stress, which decreased (−0.34 versus 0.12 kPa/y). These findings suggest that increases in intima-media thickness in young adults with the MetS may primarily reflect an adaptive mechanism that attempts to restore local hemodynamic conditions to an equilibrium rather than atherosclerosis, per se. However, carotid adaptations did not restore circumferential wall stress to levels comparable with those of the reference group, and, therefore, outward remodeling was maladaptive. Importantly, individuals who recovered from the MetS restored carotid properties to levels comparable to the reference group, emphasizing the potential for reversibility. **(*Hypertension*. 2012;60:542-549.)** ● **Online Data Supplement**

Key Words: metabolic syndrome ■ carotid remodeling ■ longitudinal study ■ young adults

Individuals with the metabolic syndrome (MetS), that is, clustering of elevated blood pressure (BP), central obesity, dyslipidemia, and impaired glucose metabolism, have an increase risk of incident cardiovascular disease, in particular, stroke.[1] However, the underlying pathophysiology of the MetS-stroke relationship remains poorly understood.

Numerous studies have linked the MetS to increased carotid intima-media thickness (IMT)[2] and or stiffness,[3] and both higher levels of carotid IMT and stiffness predict incident cardiovascular disease, in particular, stroke.[4,5] Maladaptive arterial remodeling may also constitute a mechanism linking the MetS to increased risk of stroke. Arterial remodeling, that is, the change of structural arterial properties over time in response to hemodynamic and/or metabolic factors operating within the arterial environment, is thought to be an adaptive mechanism aiming at keeping shear stress within certain limits.[6] It is characterized by widening of the interadventitial diameter (IAD) and increases in IMT. This process is considered to be maladaptive when, despite remodeling, circumferential wall tension (CWT) and stress (CWS; also designated as tensile stress) remain elevated. Maladaptive arterial remodeling has been linked to stroke by the observation of higher carotid CWT at the affected side of stroke patients.[7] Evidence thus far suggests that the MetS is associated with maladaptive arterial remodeling, but this is limited because it derives from cross-sectional studies only,[8–12] not

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all of which reported on CWT and/or CWS together with IAD, lumen diameter (LD), and IMT.[10–12]

As snap-shots, cross-sectional studies do not enable a full appreciation of dynamic processes, such as that of arterial remodeling. For example, increases in IMT could precede and lead to subsequent increases in IAD and/or LD, or, alternatively, increases in IMT could result from increased IAD. A longitudinal study is, thus, necessary for a better understanding of the temporal relationships between carotid IMT and diameter. In addition, the appreciation of accompanying (changes in) levels of CWT and CWS can elucidate the extent to which any such observed pattern of arterial remodeling is maladaptive. In view of these considerations, we have examined changes in carotid artery structural and functional properties and local hemodynamic forces as a function of changes (in clustering of traits of) MetS status, in a 6-year longitudinal study among apparently health adults.

Methods

Study Design and Population

Data were derived from the Amsterdam Growth and Health Longitudinal Study, an ongoing observational longitudinal study that started in 1976 with a total inclusion of 698 boys and girls (mean age, 13.1±0.8 years), as described in detail elsewhere.[13] In the year 2000, when subjects' mean age was 36.6 years (±0.6 years), measurements of large artery properties by means of noninvasive ultrasound were included for the first time in this cohort and obtained in 373 subjects (baseline data of the present study).[14–17] In 2006, follow-ups of arterial measurements were obtained in 297 of these individuals, 293 of whom had complete data on carotid artery properties and traits of the MetS at both time points (the sample of the present study). However, baseline characteristics from the 80 individuals without complete follow-up data did not differ from those included (data not shown). Throughout the longitudinal period, anthropometric (body height, weight, and waist circumferences), biological (blood lipids and BP), and lifestyle (smoking status, alcohol consumption, and physical activity levels) variables were assessed according to standard procedures, as detailed elsewhere.[14–17] The medical ethical committee of the VU University Medical Center in Amsterdam approved the study, and all of the participants gave written informed consent.

Carotid Artery Properties and BP

At baseline and at follow-up, carotid properties were obtained by means of the same protocol and ultrasound equipment, as described in detail previously (please see online-only Data Supplement).[14–17]

LD was calculated as IAD−(2 · IMT) and the arterial wall cross-sectional (CSA_{IMT}) as $\pi \cdot IMT \cdot (IMT+LD)$; CWT and CWS were estimated according to Laplace's law as MAP · (LD/2) and CWT/IMT, respectively, where MAP is mean arterial pressure.[8,9,18,19] The Young's elastic modulus (YEM) was estimated as IAD/(IMT · DC), where DC indicates the distensibility coefficient, which was calculated from IAD, distension, and local pulse pressure.[14–17]

Throughout the entire period of ultrasound imaging, systolic (SBP), diastolic (DBP), and MAP were assessed in the left arm at 5-minute intervals with oscillometric devices. Brachial pulse pressure was defined as SBP−DBP, and pulse pressure at the level of the carotid artery was calculated by calibration of the diameter-distension waveforms obtained at this and the brachial arteries, as described by Van Bortel et al.[20]

Definition of the MetS and Changes in MetS Status Over Time

At follow-up, subject levels of BP were obtained during the arterial assessments only, that is, while subjects were in supine position. We, therefore, deemed the use of the SBP/DBP cutoff values proposed by established definitions of the MetS (eg, National Cholesterol Education Program/International Diabetes Federation) inappropriate, because these are based on readings in the sitting position, which are higher. In addition, levels of fasting plasma glucose were not available at baseline, and, therefore, we used glycated hemoglobin (HbA1c) as a marker of glucose metabolism instead. The presence of MetS traits was defined on the basis of the highest sex-specific quartiles of SBP or DBP, waist circumference, triglycerides, and HbA1c and the lowest sex-specific quartile of high-density lipoprotein cholesterol, as measured at baseline. The cutoff values thereby derived are presented in Table S2 (available in the online-only Data Supplement) and were used to classify presence or absence of MetS traits at follow-up. Subjects were then assigned to 4 categories according to the number of traits present, that is, 0, 1, 2, and ≥3, and the latter category was used to identify individuals' clustering of traits indicative of the MetS (hereafter referred as "with MetS"). Subjects were classified further into the following 4 groups of changes in MetS status, including never (no MetS at baseline and follow-up; n=207), incident (MetS at follow-up but not at baseline; n=31), recovery (MetS at baseline but not at follow-up; n=23), and persistent (MetS at both baseline and follow-up; n=32).

Statistical Analysis

We first examined the validity of the classification of participants' MetS status as adopted herein by testing whether the observed clustering of ≥3 traits occurred at levels above those that could be dictated by chance alone.[21] This was confirmed by an observed prevalence of the MetS at baseline that was twice higher that which could be expected by chance alone (Figure S1).

Generalized estimating equations, which is a statistical method appropriate for analyses of repeated and, thus, correlated data,[22] were used to test differences in carotid artery properties, at baseline and at follow-up, and their changes over time between the 4 groups of changes in MetS status. Groups were included in these analyses as a dummy variable and differences tested relative to the reference group (never); differences in changes, also relative to the reference group, were tested by means of group · time interaction terms (model specifications given in the online-only Data Supplement). All of the analyses were adjusted for sex, height (as time-independent covariates), and age, smoking, alcohol consumption, physical activity, low-density lipoprotein cholesterol, and use of antihypertensive medication (as time-varying covariates).[22]

All data are reported in men and women combined, because we did not find any consistent significant interactions with sex. Triglycerides levels, which were positively skewed, were $\log_e$ transformed before all data analyses. Statistical significance was set at $P<0.05$, and all analyses were carried out with the use of the STATA software package version 11.2 (STATA Corp, College Station, TX).

Results

General characteristics of the study population, at baseline and follow-up, are shown in Table 1, stratified by categories of change in MetS status.

Carotid Properties and Their Changes by Categories of Change in MetS Status

At baseline, individuals with persistent MetS had significantly higher levels of IAD, LD, CWT, CWS, and YEM, but not of IMT, than those who never developed the MetS (Table 2 and Figure). In the course of follow-up, the persistent MetS group displayed significantly steeper increases in IMT (0.011 versus 0.005 mm/y), CSA_{IMT} (0.38 versus 0.14 mm^2/y), IAD (0.077 versus 0.032 mm/y), and LD (0.055 versus 0.023 mm/y), whereas changes in CWT (0.33 versus 0.27 kPa/y), CWS (−0.34 versus 0.12 kPa/y), and YEM (0.010 versus 0.002 10^3 · kPa/y) did not significantly differ from those

Table 1. Characteristics of the Study Population at Baseline and at Follow-Up by Categories of Changes in Metabolic Syndrome Status

		Metabolic Syndrome Status			
Characteristics	Time	Never (n=207)	Incident (n=31)	Recovery (n=23)	Persistent (n=32)
Male sex, %		44.9	54.8	52.2	50.0
Age, y	Baseline	36.5±0.6	36.3±0.7	36.8±0.5	36.7±0.6
	Follow-up	42.6±0.6	42.4±0.7	42.8±0.6	42.7±0.6
Traits of the metabolic syndrome					
Systolic blood pressure, mm Hg	Baseline	113.6±10.3	120.2±10.7	121.3±8.7	126.9±14.6
	Follow-up	113.5±10.1	124.5±15.3	117.6±11.2	125.0±17.0
Diastolic blood pressure, mm Hg	Baseline	63.1±6.5	67.6±6.9	69.2±6.2	71.1±7.5
	Follow-up	68.7±7.8	75.7±7.9	71.2±6.1	75.1±7.6
Waist circumference, cm	Baseline	75.7±7.8	81.5±9.7	85.1±13.2	90.2±8.2
	Follow-up	80.6±8.6	88.1±8.7	87.8±13.0	96.2±10.1
HDL cholesterol, mmol/L	Baseline	1.48±0.35	1.44±0.33	1.12±0.26	1.09±0.25
	Follow-up	1.81±0.42	1.63±0.39	1.54±0.32	1.36±0.36
Triglycerides, mmol/L	Baseline	0.9 (0.7–1.3)	1.2 (0.8–1.5)	1.7 (1.1–2.1)	1.8 (1.5–2.9)
	Follow-up	0.8 (0.7–1.1)	1.5 (1.1–2.1)	1.0 (0.7–1.2)	1.6 (1.1–2.4)
Glycated hemoglobin, %	Baseline	5.2±0.4	5.3±0.4	5.4±0.4	5.5±0.4
	Follow-up	5.3±0.2	5.7±0.9	5.4±0.2	5.6±0.3
Other risk factors					
Body mass index, kg/m^2	Baseline	23.2±2.6	24.9±2.8	26.3±3.7	28.0±3.0
	Follow-up	23.6±2.9	25.9±2.6	26.4±3.9	29.2±4.0
LDL cholesterol, mmol/L	Baseline	2.89±0.80	3.24±0.84	3.33±0.93	3.42±0.88
	Follow-up	2.70±0.74	2.89±0.94	3.25±0.93	2.94±0.78
Smokers, %	Baseline	19.8	19.4	17.4	43.8
	Follow-up	12.1	22.6	17.4	28.1
Alcohol drinkers, %	Baseline	89.4	93.5	91.3	78.1
	Follow-up	92.8	93.5	95.7	81.3
Physical activity, 10^3 METs/wk	Baseline	4.2 (2.6–6.3)	4.1 (2.2–6.4)	4.1 (3.4–6.7)	4.0 (2.6–6.5)
	Follow-up	2.7 (2.3–3.1)	2.6 (2.3–3.1)	2.6 (2.4–3.3)	2.7 (2.1–3.1)
Antihypertensive treatment, %	Baseline	1.0	0.0	4.3	9.7
	Follow-up	1.9	6.5	0.0	18.9
Carotid artery properties					
Interadventitial diameter, mm	Baseline	6.81±0.55	7.08±0.46	7.00±0.57	7.07±0.83
	Follow-up	7.01±0.62	7.31±0.56	7.20±0.55	7.51±1.00
Lumen diameter, mm	Baseline	5.57±0.54	5.79±0.46	5.78±0.58	5.79±0.79
	Follow-up	5.71±0.62	5.95±0.50	5.91±0.52	6.11±0.92
Intima-media thickness, mm	Baseline	0.62±0.10	0.64±0.10	0.61±0.06	0.64±0.12
	Follow-up	0.65±0.11	0.68±0.14	0.64±0.11	0.70±0.13
Wall cross-sectional area, mm^2	Baseline	12.1±2.3	13.0±2.2	12.2±1.6	12.9±3.2
	Follow-up	13.0±2.6	14.2±3.3	13.3±2.7	15.2±4.2
Circumferential wall tension, kPa	Baseline	29.9±4.7	32.7±4.4	33.2±5.4	34.8±7.4
	Follow-up	31.3±5.6	35.8±4.9	34.0±4.1	36.7±7.5
Circumferential wall stress, kPa	Baseline	49.1±11.4	52.1±10.8	55.5±12.5	55.9±14.2
	Follow-up	49.9±13.1	54.4±11.0	54.0±10.0	53.6±12.9
Young's elastic modulus, $10^3 \cdot$ kPa	Baseline	0.43±0.12	0.46±0.13	0.46±0.15	0.50±0.14
	Follow-up	0.44±0.15	0.52±0.14	0.50±0.14	0.56±0.20

Data are percentage, mean±SD, or median (interquartile range). LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

Table 2. Comparison of Carotid Artery Properties Across Categories of Changes in Metabolic Syndrome Status

Dependent Variable	Independent Variable: ΔMetS Status	Baseline		Follow-Up		6-y Δ	
		β	95% CI	β	95% CI	β	95% CI
IAD, mm	Incident	0.202	−0.001 to 0.405	0.247	0.045 to 0.448*	0.045	−0.097 to 0.186
	Recovery	0.137	−0.094 to 0.368	0.139	−0.093 to 0.371	0.002	−0.159 to 0.163
	Persistent	0.209	0.007 to 0.410*	0.477	−0.278 to 0.677‡	0.268	0.128 to 0.408‡
LD, mm	Incident	0.158	−0.039 to 0.353	0.187	−0.009 to 0.382	0.029	−0.121 to 0.179
	Recovery	0.164	−0.059 to 0.388	0.152	−0.072 to 0.377	−0.012	−0.183 to 0.158
	Persistent	0.183	0.002 to 0.364*	0.374	0.180 to 0.567‡	0.191	0.042 to 0.339†
IMT, mm	Incident	0.020	−0.021 to 0.061	0.029	−0.012 to 0.070	0.009	−0.032 to 0.050
	Recovery	−0.017	−0.064 to 0.030	−0.010	−0.057 to 0.037	0.007	−0.040 to 0.054
	Persistent	0.010	−0.031 to 0.051	0.051	0.011 to 0.092*	0.041	0.001 to 0.082*
CSA_{IMT}, mm^2	Incident	0.78	−0.18 to 1.73	1.09	0.14 to 2.05*	0.33	−0.53 to 1.18
	Recovery	−0.04	−1.13 to 1.06	0.14	−0.96 to 1.23	0.17	−0.80 to 1.14
	Persistent	0.63	−0.33 to 1.58	2.03	1.05 to 3.00‡	1.43	0.59 to 2.28†
CWT, kPa	Incident	2.22	0.52 to 3.92*	3.97	2.28 to 5.67‡	1.75*	0.29 to 3.21
	Recovery	3.01	1.07 to 4.96†	2.11	0.16 to 4.06*	−0.90	−2.57 to 0.76
	Persistent	5.11	3.39 to 6.84‡	5.49	3.76 to 7.22‡	0.38	−1.11 to 1.87
CWS, kPa	Incident	1.77	−2.46 to 5.99	3.75	−0.57 to 7.84	1.98	−2.28 to 6.24
	Recovery	5.77	0.94 to 10.58*	3.52	−1.31 to 8.37	−2.25	−7.10 to 2.60
	Persistent	7.21	2.91 to 11.51†	4.41	0.09 to 8.73*	−2.80	−7.11 to 1.52
YEM, $10^3 \cdot$ kPa	Incident	0.015	−0.037 to 0.067	0.068	0.016 to 0.120*	0.050	−0.008 to 0.109
	Recovery	0.018	−0.041 to 0.077	0.049	−0.011 to 0.109	0.031	−0.038 to 0.098
	Persistent	0.060	0.007 to 0.113*	0.117	0.066 to 0.168‡	0.048	−0.011 to 0.107

β indicates regression coefficient: indicates differences in carotid artery property as compared with referent group (ie, never); IAD, interadventitial diameter; LD, lumen diameter; IMT, intima-media thickness; CSA_{IMT}, wall cross-sectional area; CWT, circumferential wall tension; CWS, circumferential wall stress; YEM, Young's elastic modulus. All data are adjusted for age, sex, body height and (changes in) smoking status, alcohol consumption, physical activity, low-density lipoprotein cholesterol, and use of antihypertensive medication.

*$P<0.05$.

†$P<0.01$.

‡$P<0.001$.

observed in the reference group. Still, at follow-up CWT, CWT, CWS, and YEM remained significantly higher in the group with persistent MetS versus those who never developed the MetS. Individuals who recovered from the MetS had, at baseline, higher levels of CWT and CWS than the group who never developed the MetS but displayed favorable changes in all of the carotid artery properties such that, at follow-up, none of these differed significantly from the group who never developed the MetS. On the other hand, individuals with incident MetS displayed significantly steeper increases in CWT (0.56 versus 0.27 kPa/y) and also more adverse patterns of change in the other carotid properties (albeit not significantly different), such that, at follow-up, these individuals had significantly higher IAD, CWT, and YEM than those who never developed the MetS.

Associations Between (Changes in) MetS Traits and (Changes in) Carotid Properties

The associations of each trait of the MetS and their changes (as continuous variables) with (changes in) carotid artery properties are shown in Table 3 and can be summarized as follows. At baseline, higher levels of IAD and LD were primarily determined by higher levels of waist circumference, whereas higher levels of CWT, CWS, and YEM were determined by both higher levels of waist and BP; none of the traits of the MetS were associated with increased IMT, however. During the course of follow-up, increases in waist circumference also determined steeper increases in IAD, LD, and YEM, and increases in BP were main determinants of increases in these properties but also of CWT and CWS. Interestingly, increases in IMT were determined only by increases in HbA1c, which was also implicated in steeper increases in IAD and CSA_{IMT}. Changes in blood lipids did not affect changes in arterial properties.

Additional Analyses

When, as suggested,[23] CWT and CWS were calculated at levels of DBP instead of MAP (because IMT and IAD are measured in diastole), we observed essentially the same patterns of changes and differences across groups as reported above (please see Figure S2).

Discussion

The main finding of our study is that individuals with persistent MetS, as compared with individuals who never had the MetS, displayed significantly steeper increases in IMT and CSA_{IMT} during the course of follow-up that were preceded by elevated levels of IAD, LD, YEM, and CWT and

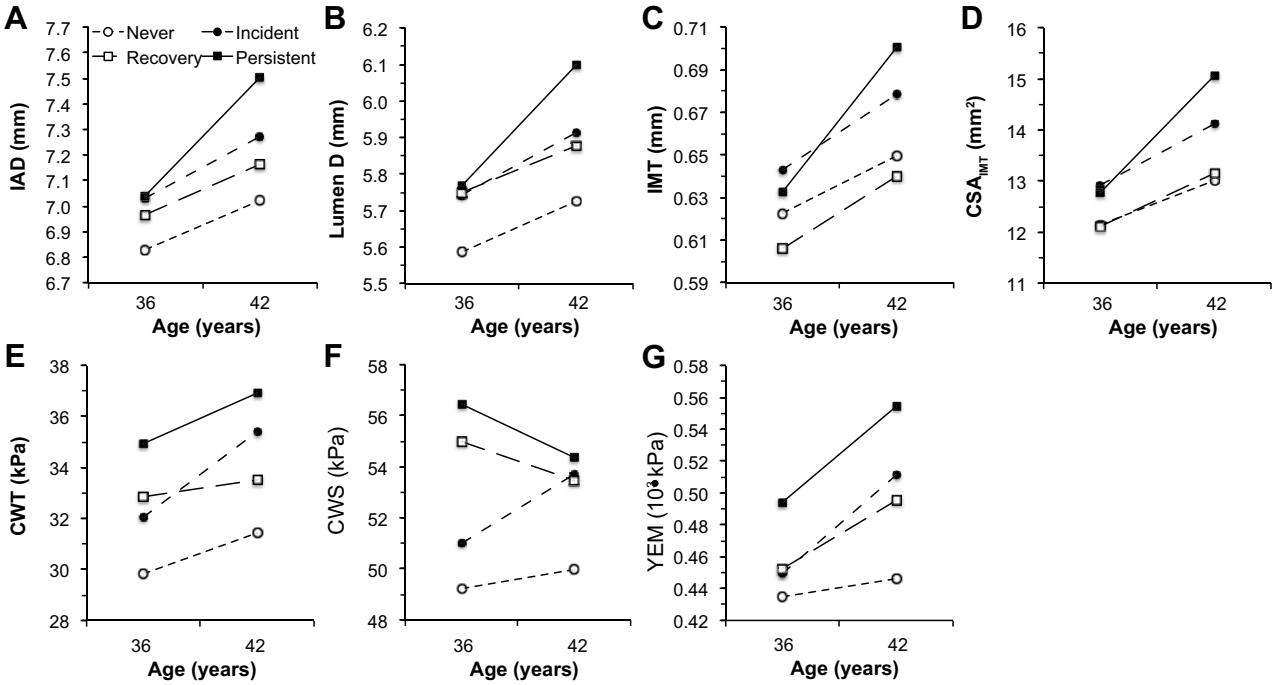

Figure. Trajectories of changes in carotid artery properties by categories of change in metabolic syndrome status. **A**, IAD indicates interadventitial diameter. **B**, LUMEN D indicates lumen diameter. **C**, IMT indicates intima-media thickness. **D**, CSA_{IMT} indicates wall cross-sectional area. **E**, CWT indicates circumferential wall tension. **F**, CWS indicates circumferential wall stress. **G**, YEM indicates Young's elastic modulus. All data are adjusted for, sex, height, and (changes in) age, smoking status, alcohol consumption, physical activity, low-density lipoprotein cholesterol, and use of antihypertensive medication; exact magnitude and statistical significance of differences between groups are given in Table 2. ○, never; ●, incident; □, recovery; ■, persistent.

CWS already at baseline. This suggests that, among young individuals without overt signs of atherosclerosis, arterial enlargement and stiffening may precede and favor subsequent wall thickening to restore normal levels of wall tensile stress. Indeed, during the course of follow-up, IAD and LD increased further, and CWS tended to decrease among individuals with persistent MetS, although it remained significantly higher than that observed in individuals who never developed the MetS. Therefore, this pattern of arterial outward remodeling remained, to an important extent, maladaptive. Notably, in individuals who recovered from the MetS, all of the carotid artery properties were restored to levels that no longer differed from those who never developed the MetS. This is an important observation, because it points toward the reversibility of a pathobiological process that, if not interrupted in time, may carry adverse health consequences, such as stroke. To our knowledge, this is the first study that has examined, with a truly longitudinal design, the life course and temporal relationships between carotid artery structural and functional properties and local hemodynamic factors as a function of changes in the MetS. Being conducted among apparently healthy and young adults, our findings likely describe the early stages of accelerated arterial aging related to the MetS.

Changes in carotid IMT and distension as a function of changes in MetS over the course of 6 years among apparently healthy adults of comparable age have been reported recently in a large (n=1673), population-based study.[24] Our findings are in agreement with this study, regarding the following: (1) the rates of changes in MetS status (never [74% versus 71%], incident [12% versus 11%], recovery [4% versus 8%], and persistent [10% versus 11%], respectively); (2) the patterns of changes in MetS traits (eg, steeper increase in DBP than SBP), even those that, at first glance, could seem counterintuitive (eg, overall increases in mean levels of high-density lipoprotein cholesterol with aging); and (3) the patterns of changes in IMT that were also steeper in those with persistent MetS only. We, thus, believe our findings, despite having been obtained with an adapted criterion to define MetS and in a smaller sample, do reflect true MetS-related arterial changes that occur in the course of young adult life. Data on concomitant changes in arterial diameter and hemodynamic forces were not provided in that study, however, thus not enabling the appreciation of MetS-related arterial remodeling processes.

Our study investigated these variables and raised the question of whether increases in IMT in the context of persistent MetS reflect atherosclerosis, concluding that wall thickening could primarily reflect an adaptive mechanism that attempted to restore local hemodynamic conditions to an equilibrium rather than atherosclerosis, per se. Indeed, it has been proposed that, at levels <0.9 mm, increases in IMT may reflect adaptive arterial remodeling.[6,25] Still, because the observed pattern of outward remodeling was maladaptive, our findings may have implications for cardiovascular risk, particularly stroke. Indeed, 3 different patterns of arterial remodeling have been identified: inward (decrease in LD resulting from greater increase in IMT than IAD), outward (increase in LD because of greater change in IAD than IMT), and compensatory (LD preservation despite changes in IAD and IMT).[26] Of these, inward and outward have been linked to

Table 3. Associations Between (Changes in) Each Metabolic Syndrome Trait and (Changes in) Carotid Artery Properties

		Dependent Variable						
Independent Variable	Time	IAD, mm	LD, mm	IMT, mm	CSA_{IMT}, mm^2	CWT, kPa	CWS, kPa	YEM, $10^3 \cdot$ kPa
Systolic blood pressure	Baseline	−0.005	−0.016	0.008	0.15	2.62‡	3.81‡	0.039‡
	Follow-up	0.091‡	0.070†	0.015†	0.52‡	3.51‡	4.30‡	0.078‡
	Δ per y	0.016‡	0.014†	0.001	0.06*	0.15‡	0.08	0.006‡
Diastolic blood pressure	Baseline	0.035	0.018	0.010	0.27*	2.74‡	3.85‡	0.040‡
	Follow-up	0.094‡	0.085‡	0.008	0.36†	3.68‡	5.23‡	0.074‡
	Δ per y	0.010*	0.011†	−0.000	0.02	0.16‡	0.23*	0.006‡
Waist circumference	Baseline	0.066*	0.058*	0.005	0.23	1.19‡	1.81†	0.019*
	Follow-up	0.118‡	0.102‡	0.009	0.46†	1.51‡	1.74†	0.045‡
	Δ per y	0.009*	0.007*	0.001	0.04	0.05	−0.01	0.004†
HDL cholesterol	Baseline	−0.018	−0.021	0.001	−0.01	−0.43	−0.78	−0.008
	Follow-up	−0.002	−0.012	0.004	0.05	−0.39	−0.75	−0.011
	Δ per y	0.003	0.002	0.001	0.01	0.01	0.00	−0.000
Ln-triglycerides	Baseline	−0.005	0.005	−0.003	−0.06	0.58*	1.23*	0.014
	Follow-up	0.040	0.053*	−0.004	0.03	0.60†	1.13	0.023†
	Δ per y	0.008	0.008	−0.000	0.02	0.00	−0.02	0.002
Glycated hemoglobin	Baseline	−0.034	−0.014	−0.007	−0.22	−0.19	0.27	0.000
	Follow-up	0.016	0.003	0.005	0.13	0.10	−0.27	0.005
	Δ per y	0.009*	0.007	0.002*	0.06*	0.05	−0.09	0.001

Data are standardized regression coefficients and indicate the differences in carotid artery property per SD increase in MetS trait; this enables comparison of the strength of the associations with carotid properties between traits; IAD, interadventitial diameter; Ln, natural logarithm; HDL, high-density lipoprotein; LD, lumen diameter; IMT, intima-media thickness; CSA_{IMT}, wall cross-sectional area; CWT, circumferential wall tension; CWS, circumferential wall stress; YEM, Young's elastic modulus. All of the data are adjusted for age, sex, body height and (changes in) smoking status, alcohol consumption, physical activity, low-density lipoprotein cholesterol, and use of antihypertensive medication.

*$P<0.05$.

†$P<0.01$.

‡$P<0.001$.

stable and unstable plaque formation, respectively.[26,27] In addition, among several carotid geometric patterns, a pattern of hypertrophy with dilation, which is, thus, equivalent to the outward remodeling described in the present study, was also linked to the highest incidence of cardiovascular disease among elderly participants of the Cardiovascular Health Study.[28] Although the extent to which young adults with the MetS showing signs of maladaptive outward remodeling are more likely to develop such kind of atherosclerotic complications later in life is not known, these observations emphasize the clinical relevance of our findings. It further stresses the potential need for early preventive measures, because we observed that recovery from MetS led to reversibility of maladaptive outward remodeling. This resulted from beneficial changes in MetS traits, in particular, DBP, waist circumference, and HbA1c (Table S3 and Figure S3), all of which contributed also to arterial adaptations (Table 3).

Because of the longitudinal design, we obtained a better insight into the sequence of carotid structural and functional adaptations related to the MetS. The observation that persistent MetS was not only associated with increased IAD and LD but also YEM (a marker of the elastic properties of the arterial wall material) already at baseline, suggests that loss of elasticity at the level of the media layer (ie, arteriosclerosis) could explain the arterial enlargement of individuals with the MetS. Consequently, the subsequent increases in IMT and CSA_{IMT} could reflect wall changes occurring primarily at the level of the media rather than the intima (atherosis) layer.

Increases in CSA_{IMT} (although not IMT) were related to changes in SBP, and increases in IAD and LD were associated with both changes in SBP and DBP but more strongly with the former than the latter (Table 3). This points toward a stronger impact of the pulsatile component of BP on arterial remodeling. Indeed, when we additionally examined the extent to which the steeper increases in IAD, LD, IMT, and CSA_{IMT} observed among individuals with persistent MetS could be explained by concomitant changes in BP, we observed that these were not affected when further adjusted for changes in DBP but were somewhat attenuated when adjusted for changes in local pulse pressure (Table S4). Transmural pressure exerts a fatiguing effect on the load-bearing elements of the arterial wall (ie, elastin and collagen), leading to degenerative changes and fracture of the extracellular matrix component that result in arterial enlargement.[23] Nevertheless, the steeper increases in IAD, LD, IMT, and CSA_{IMT} in individuals with persistent versus never MetS remained statistically significant after adjustments for BP, suggesting that other factors may be involved. Indeed, we observed that increases in these arterial properties were also determined by changes in HbA1c. This could reflect underlying cross-links between molecules in the arterial wall because of advanced-glycation end products, thereby contrib-

uting directly to accelerated arterial stiffening, as commonly observed among patients with (pre)diabetes mellitus.[3] However, HbA1c was not related to YEM, a marker of the intrinsic elastic wall material. In addition, metabolic factors related to central adiposity, yet another MetS trait related to changes in IAD, LD, and YEM, can also play an additional disrupting role in the intricate process of arterial remodeling. These may include adipocytokine or systemic inflammatory factors, oxidative stress, vascular smooth muscle cell growth, and stimulation of the sympathetic nervous system.[3,16] All together these observations suggest that clustering of elevated BP, abdominal obesity, and impaired glucose metabolism may constitute a phenotype with the most adverse impact on arterial properties. This is in line with earlier cross-sectional observations,[9] but because of the relatively small sample of the present study, we could not examine arterial changes associated with specific clusters of MetS traits further.

There are additional limitations to our study. First, ultrasound does not distinguish the intima from the media layers of the carotid wall, thus not enabling full insight on whether wall thickening related to MetS was particularly associated with atherosis (intima) or arteriosclerosis (media). Second, IMT was measured at one arterial site, and although we took measures to ensure that follow-up examinations did not differ from baseline in this regard, at both time points, our measures do not capture possible variability in IMT along the arterial wall. Third, although good levels of reproducibility were obtained between observers involved in the baseline (I.F.) and the follow-up (F.S.) examinations, data on changes in arterial properties may have been obtained with some error. If anything, this may have led to an underestimation of the associations reported herein, because both at baseline and at follow-up observers were unaware of participants' metabolic risk profiles (ie, nondifferential error). Fourth, the prevalence of the MetS as reported herein may not compare directly with that obtained with standard definitions, because it was estimated on the basis of risk factor distribution within the study population. Still, it served the purpose of identification of a phenotype (clustering of elevated MetS traits) and its change over time, which is suitable for the study of an etiologic research question, that is, its association with arterial remodeling. Last, our findings were obtained in relatively young and apparently healthy white adults and should be interpreted with caution with regard to older and higher-risk populations and other ethnicities.

Perspectives

We identified a pattern of outward carotid remodeling (ie, diameter widening and wall thickening, in this order) among individuals with persistent versus never MetS over the course of 6-year follow-up. This process was maladaptive because, despite remodeling, wall tensile stress was not restored to levels comparable to those who never had the MetS. Importantly, reversibility of maladaptive outward remodeling was achieved by recovery from the MetS. Maladaptive carotid remodeling may carry important implications for cardiovascular risk, particularly stroke. Prospective studies investigating the link between patterns of arterial remodeling in young adults with future cardiovascular outcome are further needed, to decide on the usefulness of screening and implementation of appropriate preventive measures likely to deter related cardiovascular sequelae.

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Disclosures

None.

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Novelty and Significance

What Is New?

- We studied changes in carotid structural, functional, and local hemodynamic factors as a function of changes in MetS status over the course of 6-years follow-up.
- Given the longitudinal design, we could examine the temporal relationships between diameter and wall thickening and concomitant hemodynamic factors.

What Is Relevant?

- We observed the development of a pattern of maladaptive outward carotid remodeling among individuals with persistent MetS and a similar trend among individuals with incident MetS.
- Recovery from the MetS restored initial adverse carotid adaptations to levels comparable to those who never developed the MetS. Wall thickening was preceded by wall widening.

Summary

The development of maladaptive outward remodeling may explain the increased risk of cardiovascular disease, in particular, stroke, in individuals with the MetS.